Remarks

Claims

Claims 1-34 were pending. Claims 8, 10, 11, and 13-34 have been withdrawn. Claims 1-7, 9, and 12 are under examination. Claim 6 is currently amended by deleting the term "35," which was a typographical error. Claim 11 is currently amended by deleting the term "20," which was a typographical error. Claim 11 also is currently amended to recite that the step of adding a gene by electroporation includes adding "genes that encode" alpha and accessory subunits of "an" L-type calcium "channel." Support is found at least at paragraphs 0025 and 0034 of the application as published. Claim 12 similarly is amended to recite adding "genes that encode" alpha and accessory subunits of "an" L-type calcium channel.

Rejections

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 6, 7, 9, and 11-12 were rejected as indefinite in view of the claim 6 term "35." This term has been deleted from claim 6, so the rejection should be withdrawn.

Rejection of Claims 1-7 and 9 Under 35 U.S.C. § 103

Claims 1-7 and 9 are rejected as obvious over U.S. Patent No. 6,690,970 ("Taheri") in view of U.S. Patent No. 6,387,369 ("Pittenger"). Applicants traverse and maintain that creating an atrioventricular bypass tract as recited in the pending claims is not obvious over the cited references. In this regard, it should be noted that the pending claims more particularly recite that the atrioventricular ("AV") bridge is created by "growing mesenchymal stem cells into a strip" and "attaching one end of the strip onto the atrium of the heart" while the other end of the strip is attached to "the ventricle of the heart," so that electrical signals generated by the sinus node can be propagated across the tract to excite the ventricle. As made clear in the specification (*see, e.g.*, application at 3), the tract serves to take over and "bypass" a diseased AV node. Hence, the recited bridge is created by attaching the strip to healthy atrium and ventricle tissue at each end, bypassing the damaged AV node. Applicants submit that the claim-recited method of creating a bypass tract is not taught or suggested by the cited art.

According to the Examiner, "Taheri et al teach a biological pacemaker and implantation catheter for restoring normal or near normal heartbeat function without a mechanical pacemaker. The biological pacemaker is provided by a bridge of implantation cells, that are introduced into an area of electrical malfunction, such as an impaired SA node or a blocked AV node (see abstract)." Office Action at 6. "However, Pittenger et al teach a method for producing cardiomyocytes in vivo by administering to the heart a cardiomyocyte producing amount of mesenchymal stem cells. These cells can be administered as a liquid injectable or as a preparation of cells in a matrix which is or becomes solid or semi-solid (see abstract). The reference further teaches the use of liquid cell treatment and matrix cell support treatment. The reference teaches that the MSCs are administered in a biocompatible medium which is, or becomes in situ at the site of myocardial damage, a semi-solid or solid matrix." *Id.* at 7.

The reasons set forth in Applicants' previous Response are relevant to the pending rejections and are here set forth as part of the basis for traversal. First, the claimed method clearly departs from any procedure disclosed by Taheri for treating AV block. As indicated, the claimed method entails growing a strip of cells in vitro, then implanting the strip of cells in the heart by attaching one end of the strip to healthy tissue in the atrium and attaching the other end to healthy tissue in the ventricle, bypassing the damaged AV node. In contrast, Taheri teaches implanting cells in <u>damaged</u> tissue in the heart and permitting the cells to proliferate outward to establish a connection between the atrium and the ventricle. *See, e.g.*, Taheri at col. 6, ll. 8-10 (referring to "[a]n implantation catheter **60** for mapping the block site **30** and injecting the implantation cells **26** therein") and at col. 5, ll. 59-60 ("the implantation cells **26** grow to form a conductive cell bridge **50**"). The Examiner expressly concedes that Taheri's procedure entails implanting cells at an area of electrical malfunction, such as a blocked AV node. *See* Office Action at 6. Thus there are clear differences between Taheri's teaching and the currently claimed invention.

Pittenger does not compensate for the deficiencies in Taheri. The Examiner concedes that Taheri "does not teach culturing the cells in strips and suturing," and therefore differs from the claims. Office Action at 6. The Examiner nonetheless asserts that Pittenger compensates for the deficiency by teaching the administration of mesenchymal stem cells to the heart "as a liquid injectable or as a preparation of cells in a matrix which is or becomes solid or semi-solid (see abstract). The reference further teaches the use of liquid cell treatment and matrix cell support treatment." *Id.* at 7. "[T]herefore, it can be formed into

strips that mimic the size of the ventricular valve, thus would allow ingrowth of the appropriate host cells and renewal of tissue over time (see column 1, lines 28-31)." *Id.* at 7-8.

Pittenger fails to remedy the deficiencies of Taheri. Taheri would only lead one to implant cells in damaged tissue, providing at most an outgrowth of cells to atrium and ventricle, which is distinct from attaching a bridge to healthy tissue as in the claim-recited method, as noted above. Pittenger seeks to regenerate or renew damaged tissue, not bypass it. *See, e.g.*, Pittenger at col. 1, ll. 60-64 (outlining procedure that entails implanting MSC "into the damaged heart" and "in situ formation of myocardium"). Thus, neither reference teaches or suggests attaching a strip of cells to healthy tissue in order to bypass the damaged tissue, as recited by the pending claims.

Applicants further wish to point out that the Examiner continues to improperly rely on the assertion that Pittenger *et al.* "teach producing an atrioventricular bypass tract" and improperly bases the rejection in part on this alleged disclosure. Office Action at 7 (¶ 11). The Examiner has not identified a single passage in Pittenger that teaches producing an atrioventricular bypass tract.

Further, while it is clear that Pittenger does not teach or suggest repair, replacement, or provision of an AV bridge, it is equally clear that Pittenger is instead concerned with the wholly distinct goal of restoring contractile muscle function, thereby improving the heart's pumping activity. This would have been understood by the person of ordinary skill in the art at the time of filing. Thus, Pittenger states that "[i]n accordance with the present invention mesenchymal stem cells (MSCs) are used to regenerate or repair striated cardiac muscle." Pittenger at col. 1, ll. 42-44 (emphasis added). Further, the "MSCs differentiate into cardiac muscle cells and integrate with the healthy tissue of the recipient to replace the function of the dead or damaged cells, thereby regenerating the cardiac muscle as a whole." *Id.* at col. 1, ll. 45-48. A principle step in Pittenger's method is "in situ formation of myocardium" (*see* Pittenger at col. 1, ll. 60-64), that is, the tissue that mechanically causes blood to flow by its rhythmic contraction and relaxation. *See* Arnold M. Katz, Physiology of the Heart p. 15-19 (4th ed. 2006) ("Katz," Exhibit A).[1] Pittenger therefore further teaches steps to be taken to promote the differentiation of the stem cells into muscle cells, such as "genetically

[1] According to Katz, "working myocytes" are "specialized for contraction" and are "filled with cross-striated myofibers and mitochondria," whereas the "nodal cells" of the AV node (a "network[ ] of small, sparsely cross-striated cells") are responsible for "atrioventricular conduction delay" and are "rich in glycogen and contain few contractile filaments." Katz at 15, 17, 18 and Fig. 1-11.

modif[ying] or engineer[ing the MSCs] to contain genes which express proteins of importance for the differentiation and/or maintenance of striated muscle cells" (emphasis added). Pittenger at col. 2, ll. 51-54. Pittenger thus teaches that the method is useful to treat, for example, cardiac infarct by creating new muscle in the infarct zone. *See id.* at col. 4, ll. 7-19.

The reference to "conductive tissue regeneration" (Pittenger at col. 1, ll. 54-55) in this context would have been understood by the person of ordinary skill in the art to refer merely to regeneration of heart muscle and not to have any relevance to AV node function. "[T]he heart functions as if all of the myocytes are in free electrical communication." Arnold M. Katz, Physiology of the Heart 18 (4th ed. 2006).

Also, any reference by Pittenger to a valve is irrelevant to the atrioventricular node or to the claimed method of creating an atrioventricular bypass tract, as detailed in Applicants' previous response. An atrioventricular bridge permits conduction of electrical signals from the atrium to the ventricle (see application as published ¶ 0012), and is therefore wholly distinct in structure and function from a valve, which permits blood to flow from one heart chamber to the next. *See, e.g.*, Arnold M. Katz, Physiology of the Heart pages 3-10 and page 9 Figure 1-6 (4th ed. 2006) (diagram of heart illustrating tricuspid valve as wholly separate from AV node and AV bundle) (Exhibit A). The Examiner appears to erroneously equate heart valves with the heart's AV node, and therefore inappropriately bases the obviousness rejection on Pittenger's discussion of heart valves (*see* Office Action at 7 (bottom) and at 8 (top)).

In sum, the Examiner has not properly understood Pittenger and, as a consequence, has erroneously concluded that the person of ordinary skill in the art would have been motivated to combine Pittenger and Taheri. First, the Examiner explicitly relies on Pittenger teaching an AV bridge as a basis for finding a motivation to combine. Pittenger contains no such teaching. Second, Pittenger and Taheri have wholly distinct goals (repair of heart muscle by the former vs. treating damaged SA or AV node by the latter). As a result, the person of ordinary skill in the art would not have been motivated to combine the teachings of these two references. In the absence of a motivation to combine, there is no *prima facie* obviousness and the Examiner's obviousness rejection should be withdrawn.

Also, the Examiner appears to rely on Pittenger's reference to sutures as teaching or suggesting the limitation of claim 2 "wherein the steps of attaching are performed by suturing." *See* Office Action at 7 (¶ 10), citing Pittenger at col. 6, ll. 30-37. This reliance is in error because Pittenger clearly refers to the use of sutures to close an incision after performing an operation on rats (*see* Pittenger col. 6, ll. 23-32 and 34). This is completely distinct from and irrelevant to the claim-recited step of attaching the atrioventricular bypass tract of cells to the heart by means of sutures. The rejection of claim 2 should be withdrawn for this additional reason.

Applicants further note that they fail to understand the Examiner's statement beginning at the bottom of page 7 of the Office Action: "One of ordinary skill in the art would have been motivated to combine, since Pittenger teach the use of liquid or matrix, therefore, it can be formed into strips that mimic the size of the ventricular valve, thus would allow ingrowth of the appropriate host cells and renewal of tissue over time." This appears to employ impermissible hindsight in stating that the liquid or matrix "can be formed into strips," since the Examiner does not point to any teaching or suggestion that the liquid or matrix are or should be formed into strips. Further, as noted above, the Examiner states that the strips "mimic the size of the ventricular valve." This compounds the error, since a ventricular valve is wholly distinct in form and function from the atrioventricular node. The motivation to combine cannot properly rest on these errors, and the rejection should be withdrawn.

Applicants also point out that, according to the claimed method, the bypass tract is grown in vitro and then placed into the heart, one end attached to the atrium and one end attached to the ventricle, without the need for further cell proliferation or differentiation. In contrast, Taheri teaches implantation of cells into the heart that subsequently grow in situ to compensate for damaged or absent structures (*see, e.g.*, Taheri at col. 3, ll. 7-10 ("The implantation cells grow to form a conductive cell bridge around the malfunction area.")) and Pittenger teaches implantation of cells that differentiate and/or proliferate in order to provide otherwise missing or damaged structures (*see, e.g.*, Pittenger at col. 1, ll. 45-46 ("[t]he MSCs differentiate into cardiac muscle cells") and at col. 2, ll. 41-45 (the matrix "enhances the opportunity for the administered MSCs to proliferate, differentiate and eventually become fully developed cardiomyocytes")). The person of ordinary skill in the art therefore would not have been motivated to combine Pittenger with Taheri, and, further, Pittenger would not have motivated the person of ordinary skill in the art to modify Taheri to arrive at the claimed

invention. In view of the above, Applicants respectfully request that the rejections of claims 1-7 and 9 be withdrawn.

Rejection of Claims 1-7, 9 and 12 Under 35 U.S.C. § 103

Claims 1-7, 9, and 12 are rejected under 35 U.S.C. § 103 over Taheri in view of Pittenger and U.S. Pat. App. Pub. No. 2002/0155101 ("Donahue"). Applicants traverse and request withdrawal of the rejection.

First, Donahue does not teach or suggest the preparation of an AV bypass bridge, or the use of mesenchymal stem cells to prepare an AV bypass bridge, or any of the other limitations addressed above. The Examiner apparently implicitly concedes this, and invokes Donahue only for the alleged teaching or suggestion to treat a cardiac arrhythmia using genes that encode, *inter alia*, alpha and accessory subunits of an L-type calcium channel. *See* Office Action at 8-9 (¶¶ 12-14). Since Donahue therefore does not compensate for the deficiencies of Taheri and Pittenger set forth above, the claims should not be considered *prima facie* obvious over the combination of Taheri, Pittenger, and Donahue

Second, the person of ordinary skill in the art would not have been motivated to combine Donahue with Taheri or Pittenger or the two in combination. Taheri is concerned with preparing a bridge using, preferably, autologous AV or SA node cells alone or in combination with other cells. *See* Taheri at col. 3, ll. 2-10. The SA or AV node cells may be modified by "transvect[ion]" with various nucleic acids. *See id.* at col. 5, ll. 34-42. Pittenger is concerned with heart muscle repair and does not refer to or suggest bridges. Donahue is concerned with treating cardiac arrhythmias generally (*see* Donahue ¶¶ 0013 and 0094) and further teaches the direct introduction of nucleic acids encoding various proteins into the cells of the heart (*see* Donahue ¶¶ 0003 and 0095-0101). Thus, while Donahue indicates that arrhythmia generally can be treated with ion channels, Donahue neither teaches nor suggests the use of a bridge to treat an arrhythmia, and does not teach or suggest the modification of the cells of the bridge to promote the cells' function as a bridge. The person of ordinary skill in the art therefore at least would not be motivated to combine Donahue with Taheri to modify the bridge of Taheri. The combination of Donahue with Pittenger would not have taught or suggested a modified bridge because neither Donahue nor Pittenger teaches or suggests an AV bridge. Thus, the three documents in combination would not have taught or suggested the instantly claimed invention. It can only be concluded that the instantly claimed

method of creating an atrioventricular bypass tract comprising mesenchymal stem cells modified by the introduction of a gene encoding alpha and accessory subunits of an L-type calcium channel would not have been obvious over a combination of Taheri, Pittenger, and Donahue. The rejection of the claims over this combination should therefore be withdrawn.

Conclusion

It is respectfully submitted that the presently pending claims are allowable. All issues raised by the Examiner having been addressed, an early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

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